

The need for the closer monitoring of novel drugs in MS: a Siponimod retrospective cohort study (Realhes Study)

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Table S1. Continuous and categorical variables evaluated

Continuous variables	Categorical variables
• Age at diagnosis • Age at start of siponimod • Body mass index • Basal leukocytes • Basal lymphocytes • Number of prior lines of therapy • Initial siponimod dose • Time (months) from last treatment to start of siponimod	• Sex (male/female) • Comorbidities ○ Hypertension (yes/no) ○ Autoimmune disorders (yes/no) ○ Cardiovascular disease (yes/no) ○ Respiratory disease (yes/no) ○ Liver disease (yes/no) ○ Renal impairment (yes/no) • CYP2C9 genotype ○ *1/*1 (yes/no) ○ *1/*2 (yes/no) ○ *2/*2 (yes/no) ○ *1/*3 (yes/no) ○ *2/*3 (yes/no) ○ *3/*3 (yes/no) ○ Other (yes/no) • Previous treatments received in relation to MS ○ Interferon beta 1a (yes/no) ○ Interferon beta 1b (yes/no) ○ Glatiramer acetate (yes/no) ○ Fingolimod (yes/no) ○ Ocrelizumab (yes/no) ○ Rituximab (yes/no) ○ Alemtuzumab (yes/no) ○ Mitoxantrone (yes/no) ○ Ofatumumab (yes/no) ○ Ozanimod (yes/no) ○ Posenimod (yes/no) ○ Natalizumab (yes/no) ○ Cladribine (yes/no) ○ Teriflunomide (yes/no) ○ Fumaratodimethyl (yes/no) • Concomitant treatments

	○ Inhibitors of siponimod-metabolizing cytochromes (CYP2C9/CYP3A4) (yes/no) ○ Inducers of siponimod-metabolizing cytochromes (CYP2C9/CYP3A4) (yes/no) ○ Antineoplastics (yes/no) ○ Immunomodulators (yes/no) ○ Immunosuppressants, including corticosteroids (yes/no) • Naive patients (yes/no) • Type of last treatment received prior to siponimod (first-line (Ref)/second-line/inductor) • Adequate washing period (yes/no) • Type of last treatment received prior to siponimod ○ Interferon beta 1a (yes/no) ○ Interferon beta 1b (yes/no) ○ Glatiramer acetate (yes/no) ○ Fingolimod (yes/no) ○ Ocrelizumab (yes/no) ○ Rituximab (yes/no) ○ Alemtuzumab (yes/no) ○ Mitoxantrone (yes/no) ○ Ofatumumab (yes/no) ○ Ozanimod (yes/no) ○ Posenimod (yes/no) ○ Natalizumab (yes/no) ○ Cladribine (yes/no) ○ Teriflunomide (yes/no) ○ Fumaratodimethyl (yes/no)
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Table S2. Univariate and multivariate logistic regression analysis for grade 3-4 lymphopenia and grade 4 lymphopenia.

Grade 3-4 lymphopenia		
	Univariate OR (IC 95%); p	Multivariate OR (IC 95%); p
Sex	2.836 (1.126-7.148); 0.023	3.96 (1.28-12.36); 0.017
Age at diagnosis	0.95 (0.91-0.997); 0.021	0.94 (0.89-1.020); 0.090
Age at start of siponimod	0.92 (0.89-0.998); 0.048	0.91 (0.76-1.101); 0.118
Body mass index	0.370	
Comorbidities		
Hypertension	0.651 (0.237-1.785); 0.402	
Liver disease	ND	
Renal impairment	ND	
Autoimmune disorders	2.676 (0.553-12.951); 0.206	
Cardiovascular disease	0.081 (0.009-0.698); 0.004	0.076 (0.005-1.125); 0.076
Respiratory disease	ND	
Basal CBCs		
Leukocytes x10 ³ /microL	0.075	
Lymphocytes x10 ³ /microL	1.90 (1.16-3.13); 0.011	1.63 (1.09-2.95); 0.014
CYP2C9 genotype		
*1/*1	1.055 (0.512-2.174); 0.884	
*1/*2	4.874 (1.081-7.640); 0.030	2.539 (0.565-11.414); 0.224
*2/*2	1.111 (0.098-12.595); 0.932	
*1/*3	ND	
*2/*3	ND	
*3/*3	ND	
Other	ND	
Not available	0.281 (0.095-0.832); 0.017	0.293 (0.007-1.928); 0.089
Prior treatment		
Interferon beta 1a	2.498 (1.094-5.706); 0.027	1.424 (0.448-4.528); 0.549
Interferon beta 1b	0.982 (0.395-2.439); 0.968	
Glatiramer acetate	0.541 (0.248-1.184); 0.122	
Fingolimod	0.419 (0.181-0.974); 0.040	0.277 (0.065-1.1774); 0.08
Ocrelizumab	1.117 (0.266-4.692); 0.880	
Rituximab	1.253 (0.407-3.857); 0.694	
Alemtuzumab	0.543 (0.074-3.990); 0.543	

Mitoxantrone	ND	
Ofatumumab	ND	
Ozanimod	ND	
Posenimod	ND	
Natalizumab	0.316 (0.130-0.765); 0.009	0.173 (0.046-1.291); 0.09
Cladribine	0.549 (0.034-8.984); 0.670	
Teriflunomide	0.651 (0.237-1.785); 0.402	
Fumarato dimethyl	5.494 (1.550-19.472); 0.004	6.55 (1.28-12.36); 0.017
Number of prior lines of therapy	0.729	
Initial dose	0.374	
Concomitant treatment		
Inhibitors of siponimod-metabolizing cytochromes (CYP2C9/CYP3A4)	4.145 (0.494-34.789); 0.158	
Inducers of siponimod-metabolizing cytochromes (CYP2C9/CYP3A4)	2.347 (0.477-11.549); 0.282	
Antineoplastics	ND	
Inmunomoduladores	0.628 (0.239-1.650); 0.343	
Immunosuppressants, including corticosteroids	0.646 (0.266-1.569); 0.332	
Naive patients	0.763 (0.269-1.162); 0.611	
Type of last treatment received prior to siponimod		
First-line (Ref)	-	
Second-line	0.842 (0.377-1.883); 0.676	
Inductor	0.474 (0.87-2.582); 0.474	
Adequate washing period	1.345 (0.524-3.452); 0.538	
Last treatment received prior to siponimod		
Interferon beta 1a	1.117 (0.266-4.692); 0.880	
Interferon beta 1b	1.114 (0.196-6.327); 0.903	
Glatiramer acetate	0.967 (0.268-3.496); 0.959	
Fingolimod	0.628 (0.239-1.650); 0.343	
Ocrelizumab	1.714 (0.332-8.861); 0.516	
Rituximab	1.253 (0.407-3.857); 0.694	
Alemtuzumab	0.543 (0.074-3.990); 0.543	
Mitoxantrone	ND	
Ofatumumab	ND	
Ozanimod	ND	
Posenimod	ND	
Natalizumab	1.114 (0.196-6.327); 0.903	

Cladribine	ND	
Teriflunomide	0.282 (0.078-1.022); 0.043	0.172 (0.062-1.938); 0.102
Fumarato dimethyl	9.926 (1.266-77.804); 0.009	8.837 (0.892-82.890); 0.092
Time (months) from last treatment to start of siponimod	0.244	

Grade 4 lymphopenia		
	Univariate OR (IC 95%); p	Multivariate OR (IC 95%); p
Sex	1.604 (0.439-5.855); 0.472	
Age at diagnosis	0.634	
Age at start of siponimod	0.703	
Body mass index	0.066	
Comorbidities		
Hypertension	ND	
Liver disease	ND	
Renal impairment	ND	
Autoimmune disorders	ND	
Cardiovascular disease	ND	
Respiratory disease	ND	
Basal CBCs		
Leukocytes x10 ³ /microL	0.621	
Lymphocytes x10 ³ /microL	0.329	
CYP2C9 genotype		
*1/*1	0.633 (0.176-2.277); 0.480	
*1/*2	1.926 (0.524-7.077); 0.317	
*2/*2	26.000 (2.460-314.965); <0.001	70.88 (4.37-1,150); 0.003
*1/*3	ND	
*2/*3	ND	
*3/*3	ND	
Other	ND	
Not available	ND	
Prior treatment		
Interferon beta 1a	3.831 (1.056-13.898); 0.031	3.232 (0.932-15.441); 0.098
Interferon beta 1b	1.636 (0.401-6.672); 0.489	
Glatiramer acetate	0.926 (0.232-3.703); 0.914	
Fingolimod	0.321 (0.039-2.22); 0.266	

Ocrelizumab	1.375 (0.156-12.131); 0.774	
Rituximab	0.687 (0.082-5.754); 0.727	
Alemtuzumab	3.833 (0.364-40.340); 0.231	
Mitoxantrone	ND	
Ofatumumab	ND	
Ozanimod	ND	
Posenimod	ND	
Natalizumab	1.549 (0.351-6.299); 0.538	
Cladribine	ND	
Teriflunomide	2.575 (0.614-10.795); 0.183	
Fumarato dimethyl	5.880 (1.634-21.160); 0.003	7.021 (1.452-34.051); 0.016
Number of prior lines of therapy	1.50 (1.02-2.23); 0.041	1.93 (0.831-4.243); 0.832
Initial dose	0,133	
Concomitant treatment		
Inhibitors of siponimod-metabolizing cytochromes (CYP2C9/CYP3A4)	1.586 (0.177-14.210); 0.678	
Inducers of siponimod-metabolizing cytochromes (CYP2C9/CYP3A4)	1.211 (0.139-10.555); 0.862	
Antineoplastics	ND	
Inmunomoduladores	2.228 (0.537-9.224); 0.259	
Immunosuppressants, including corticosteroids	0.918 (0.186-4.539); 0.916	
Naive patients	ND	
Type of last treatment received prior to siponimod		
First-line (Ref)		
Second-line	0.725 (0.192-2.732); 0.634	
Inductor	1.667 (0.166-16.757); 0.664	
Adequate washing period	2.258 (0.274-18.615); 0.449	
Last treatment received prior to siponimod		
Interferon beta 1a	1.375 (0.156-12.131); 0.774	
Interferon beta 1b	2.260 (0.240-21.278); 0.465	
Glatiramer acetate	ND	
Fingolimod	0.521 (0.063-4.313); 0.539	
Ocrelizumab	1.586 (0.177-14.210); 0.678	
Rituximab	0.687 (0.082-5.754); 0.727	
Alemtuzumab	3.833 (0.364-40.340); 0.231	
Mitoxantrone	ND	
Ofatumumab	ND	

Ozanimod	ND	
Posenimod	ND	
Natalizumab	2.260 (0.240-21.278); 0.465	
Cladribine	ND	
Teriflunomide	1.080 (0.125-9.321); 0.944	
Fumarato dimethyl	3.029 (0.713-12.869); 0.118	
Time (months) from last treatment to start of siponimod	0.227	

ND: not available, any of the groups n=0.